



Case report

Two cases of oral aspirin overdose

Hideaki Kato PhD Assistant Professor*, Kanji Yoshimoto PhD Associate Professor,
Hiroshi Ikegaya MD, PhD Professor

Department of Forensic Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

ARTICLE INFO

Article history:

Received 8 January 2009

Received in revised form

8 April 2009

Accepted 5 March 2010

Available online 14 April 2010

Keywords:

Acetylsalicylic acid

Aspirin

Salicylic acid

HPLC

ABSTRACT

A 30-year-old woman and a 27-year-old man were found in a parked car after the man had telephoned his father to tell him of their suicide attempt. In spite of emergent hospitalization and intensive care, the woman died. Due to the possibility of his assisting her suicide, medicolegal autopsy and toxicological analysis were performed. On forensic autopsy, no external injuries or pathological findings were detected. The man recovered after 5 days of hospitalization. In spite of a negative toxicological screening test, the police investigation revealed that they may have taken 120 tablets (330 mg/tablet; 39,600 mg total dose) of aspirin (acetylsalicylic acid) orally; therefore, we analyzed the concentrations of acetylsalicylic acid and two kinds of metabolite in specimens obtained at autopsy and on emergent hospitalization using high performance liquid chromatography. Acetylsalicylic acid and/or the two metabolites were found in the woman's specimens. These substances were also present in the man's specimens. It is still unclear why the man survived in spite of what appeared to be a fatal aspirin overdose. It was very straightforward to diagnose aspirin poisoning in these cases; however, we have to be aware of poisoning by drugs which are not included in simple drug screening examinations.

© 2010 Elsevier Ltd and Faculty of Forensic and Legal Medicine. All rights reserved.

1. Introduction

Japan has one of the highest suicide rates in the world. The number of annual suicides is presently about 30,000¹, and many involve an overdose of over-the-counter (OTC) drugs. OTC drugs can be easily obtained at local drug stores, and methods of suicide using these drugs are spread through the Internet, books and mass-media. In the present case, a couple was found in a parked car. In the police investigation, several boxes of aspirin were found beside the two victims. The woman died after arriving at the hospital, but the man survived.

Recently, simple drug screening kits such as Triage® have been developed; however, drugs that are actually detectable are limited. There is possibility that many OTC drugs are not detected by the drug screening kits. It is important to detect and quantify the concentrations of OTC drugs and related metabolites. Therefore, we investigated the concentrations of aspirin (acetylsalicylic acid) and its metabolites in the couple's specimens using a high performance

liquid chromatography (HPLC) method to verify that they had overdosed on aspirin.

2. Case presentation

A 30-year-old woman and a 27-year-old man were found in a parked car in a parking lot after the man had telephoned his father, telling him of the suicide attempt. In the police investigation, it was found that they had gotten to know each other through telephone dating club about 4 months prior to the double suicide attempt, sharing economic and physical problems. In addition, three boxes of aspirin and two boxes of DREWELL® (diphenhydramine) had been placed beside them; therefore, they could both have potentially ingested 120 tablets (330 mg/tablet; 39,600 mg total dose) of aspirin and 12 tablets of DREWELL® (25 mg/tablet; 300 mg total dose). While being transported by ambulance, the woman was unresponsive but did cry out strangely. She underwent intensive treatment involving oral charcoal administration; however, she died 22 h after ingestion. She had no prior history of allergy to the drugs. Medicolegal autopsy was performed about 18 h after her death. She was 144 cm tall and weighed 65.4 kg. The body showed marked swelling. No injuries could be detected on external and internal examination. Internally, cardiac blood (50 ml) was dark-red. Black fluid (130 ml) containing charcoal was found in the stomach. Although most of the urine did not remain in the bladder,

* Corresponding author. Present address: Department of Forensic Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan. Tel./fax: +81 75 251 5343.

E-mail address: hoi@koto.kpu-m.ac.jp (H. Kato).

it was only available for the Triage® test. The brain weighed 1100 g, and the right temporal lobe from the right forebrain was atrophic. While alive, both arms showed impaired movement because of this atrophy. As a result of alcohol analysis, it was revealed that the blood and stomach of the deceased did not contain ethanol. In addition, the Triage® test revealed no presence of drugs of abuse. On the other hand, the man recovered after 5 days of hospitalization. We had to consider the possibility that the man killed the woman and then faked the double suicide attempt. Assisted suicide is also a crime in Japan. Due to the possibility of his assisting in her suicide, a toxicological analysis of their specimens was performed in addition to the autopsy of the woman.

3. Materials and methods

3.1. Reagents and chemicals

All chemicals and solvents were of analytical grade. The drugs used in the present study were acetylsalicylic acid (Wako Pure Chemical, Osaka, Japan), salicylic acid (Wako Pure Chemical, Osaka, Japan), salicyluric acid (MP Biomedical, Illkirch, France), and *o*-toluic acid (Wako Pure Chemical, Osaka, Japan). Citric acid monohydrate, disodium hydrogenphosphate, methanol, acetonitrile and *n*-propanol were purchased from Nacalai Tesque (Kyoto, Japan). Acetylsalicylic acid, salicylic acid and salicyluric acid were used as analytical standards.

3.2. Biological materials

Immediately on arrival at the hospital, urine and serum specimens were taken following permission from the police. Post-mortem specimens of serum and the stomach contents were obtained on autopsy of the woman. The blood specimens were centrifuged (10 min, 650 × g, 20 °C) and serum was preserved. All specimens were not added any preservatives and stored at –30 °C until analysis.

3.3. Analyses of the serum, stomach contents and urine

Each specimen (300 µl) was subjected to liquid/liquid extraction. *o*-Toluic acid dissolved in methanol was added to the specimen as the internal standard at a concentration of 100 µg/ml, and then 200 µl of acetonitrile was added and the mixture was centrifuged (3000 rpm, 5 min). The supernatant was mixed with 400 µl of 0.2 M disodium hydrogenphosphate and 0.1 M citric acid buffer (pH 3.0).

3.4. HPLC conditions and detector setting

The concentrations of acetylsalicylic acid, salicylic acid and salicyluric acid were determined by HPLC using UV detection (wavelength: 254 nm). The HPLC system consisted of a DP-8020 pumping system and a CO-8020 column oven (Tosoh Co., Tokyo, Japan); column, TSKgel Super-ODS (Tosoh Co., Tokyo, Japan); column and particle size, 4.6 × 100 mm and 2 µm, respectively; eluent, 50 mM sodium dihydrogenphosphate (pH 2.5)/acetonitrile (80:20 v/v); flow rate, 1.0 ml/min; and temperature, 40 °C. UV spectra were recorded on a Chromatopac C-R8A reporting integrator (Shimadzu Co., Kyoto, Japan).

3.5. Alcohol determination and preliminary drug screening

The presence of alcohol was assessed by headspace gas chromatography.² The analytical conditions were as follows: instrument, Shimadzu GC-8A (FID detector) (Kyoto, Japan); column, glass column of 2.1 m × 3.2 mm (inner diameter) with Chromosorb W

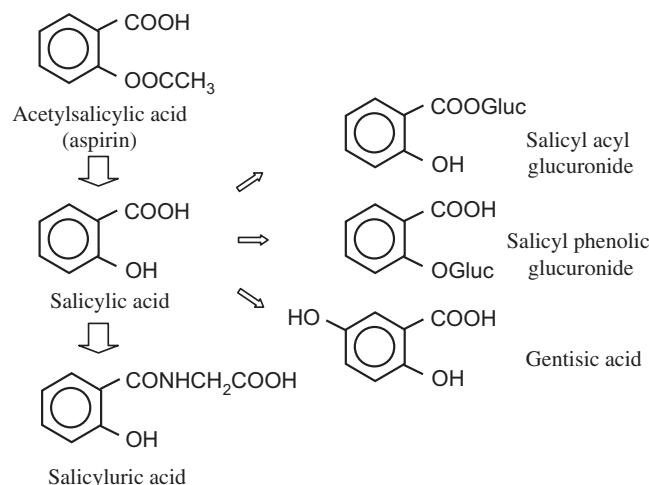


Fig. 1. Metabolic pathway of aspirin in humans. Virtually the entire dose of aspirin is hydrolyzed by esterase to salicylic acid. Nearly all of a single dose is eliminated in the urine as salicyluric acid (about 80%). –Gluc: glucuronide ($-C_6H_8O_6$).

60/80 AW-DMCS polyethylene glycol 1000 25%; column temperature, 100 °C; injection temperature, 140 °C; and internal standard, *n*-propanol. The screening of drugs was performed using the serum of the deceased with the use of Triage® (Biosite, CA, USA) for phencyclidine, benzodiazepines, cocaine, amphetamines, cannabinoids, opiates, barbiturates and tricyclic antidepressants.

4. Results and discussion

Aspirin is a nonsteroidal anti-inflammatory drug that is widely used to decrease pain and reduce swelling. It is well-tolerated and has been used effectively by millions of people for over 100 years.³ Most people in the world view aspirin as one of the safest drugs due to its broad therapeutic usage. Aspirin overdose is often a method of suicide due to its ease of availability.^{4,5} Virtually all aspirin is hydrolyzed by both the liver and blood esterases to salicylic acid, an active analgesic that accounts for most or all of the pharmacological activity of the parent drug. Usually, nearly all of a single dose is eliminated in the urine as salicyluric acid (about 80%; Figs. 1 and 2).⁶ Therefore, we investigated the concentrations of acetylsalicylic acid (aspirin), salicylic acid and salicyluric acid in their specimens (Fig. 2).

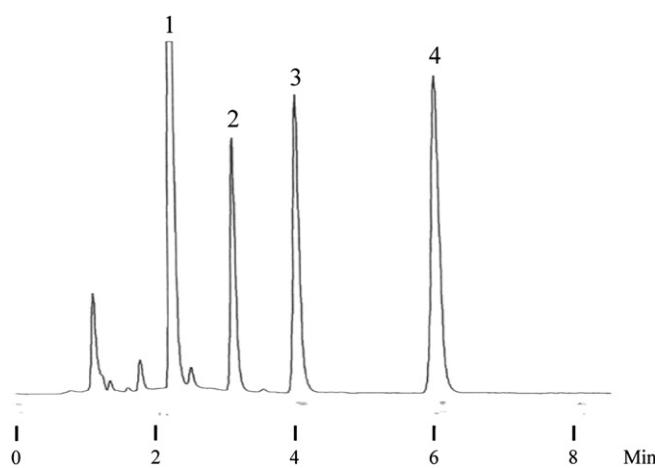


Fig. 2. HPLC-UV chromatograph obtained from spiked normal serum for salicyluric acid (peak 1), acetylsalicylic acid (peak 2), and salicylic acid (peak 3), and *o*-toluic acid as an internal standard (peak 4). The wavelength of the UV detector was set at 254 nm.

Table 1

Concentrations of acetylsalicylic acid and its metabolites in the woman's samples.

	Acetylsalicylic acid	Salicylic acid	Salicyluric acid
Samples of woman on arrival at hospital			
Serum	n.d.	0.39 mg/ml	0.003 mg/ml
Urine	0.06 mg/ml	1.25 mg/ml	0.049 mg/ml
Autopsy samples of deceased woman			
Serum	n.d.	0.24 mg/ml	0.002 mg/ml
Stomach content	0.10 mg/ml	0.20 mg/ml	n.d.

n.d., not detected.

Concentrations of salicylic acid in the woman's serum at the time of hospitalization and autopsy were 0.39 and 0.24 mg/ml, respectively (Table 1). Acetylsalicylic acid, salicylic acid and/or salicyluric acid were detected in the woman's serum, stomach contents and urine. Rehling reported that salicylic acid concentrations in the blood of 62 cases of fatal salicylate poisoning were 0.06–7.32 mg/ml, with an average of 0.66 mg/ml.⁷ The salicylic acid concentration in the woman's serum at the time of hospitalization and autopsy was within the fatal range. From these toxicological data together with autopsy findings, her cause of death was diagnosed as aspirin poisoning. Finally, from our postmortem diagnosis and the police investigation, her manner of death was determined as a suicide by the ingestion of a large quantity of aspirin.

The concentration of salicylic acid in the man's serum at hospitalization was 0.41 mg/ml (Table 2). Both salicylic acid and salicyluric acid were detected in his serum and urine. His salicylic acid concentration at hospitalization was also within the fatal range. These findings suggest that the man, suspected of assisting in her suicide, definitely ingested a large quantity of aspirin in what appeared to be a double suicide attempt.

It is well-known that many serious central nervous symptoms are caused by acute aspirin poisoning.^{8–11} There is a possibility that the woman showed high-level sensitivity to aspirin due to the functional disorder of her brain, such as atrophy, but the reason why only she died remains unclear.

Recently, books and many Japanese Internet sites describe suicide methods using OTC drugs, such as aspirin, because of its ease of availability. In the present case, they might have learnt of this suicide method through such media. It is necessary to be more careful regarding suicide and poisoning using aspirin from the aspect of emergency medication. Moreover, the present two cases may have ingested 12 tablets of diphenhydramine (300 mg total dose) with the aspirin. Diphenhydramine, an antihistamine agent, is used for improvement of sleeplessness in Japan. It is considered to be a relatively nontoxic drug excluding infants. In fact, it was reported that a 34-year-old man who took as much as 1600 mg of diphenhydramine daily did not show any apparent physical

Table 2

Concentrations of acetylsalicylic acid and its metabolites in the man's samples.

	Acetylsalicylic acid	Salicylic acid	Salicyluric acid
Samples of man on arrival at hospital			
Serum	n.d.	0.41 mg/ml	0.012 mg/ml
Urine	n.d.	2.84 mg/ml	0.467 mg/ml

n.d., not detected.

effects.¹² In the police investigation, each victim took 300 mg of diphenhydramine. Therefore, it is suggested that there was little influence of the diphenhydramine in the present case. Because from such a point of view and we paid our attention to aspirin poisoning mainly, we did not try to detect the amount of diphenhydramine in specimens using gas chromatography.

In conclusion, fatal serum concentrations of salicylic acid were found in the two cases, in which one died and the other survived. The reason for this outcome remains unclear. However, we have to be aware of poisoning by drugs which are not included in simple drug screening examinations.

Conflict of interest

None declared.

Funding

None.

Ethical approval

None.

References

- Association of public welfare statistics. Trends of health of nation, 2007. Japanese.
- The Japanese Society of Legal Medicine. Alcohol analysis. In: *Manual for forensic toxicology analysis of the Japanese society of legal medicine*. Fukuoka: Japan: Kijima Press; 1999. p. 20–1.
- Vainio H, Morgan G. Aspirin for the second hundred years: new uses for an old drug. *Pharmacol Toxicol* 1997;**81**(4):151–2.
- Ferguson RK, Boutros AR. Death following self-poisoning with aspirin. *JAMA* 1970;**213**(7):1186–8.
- James SH, Martinak JF. Recovery following massive self-poisoning with aspirin. *N Y State J Med* 1975;**75**(9):1512–4.
- Davison C. Salicylate metabolism in man. *Ann N Y Acad Sci* 1971;**179**:249–68.
- Rehling CJ. Poison residues in human tissues. In: Stolman A, editor. *Progress in chemical toxicology*, vol. 3. New York: Academic Press; 1967. p. 363–86.
- Temple AR. Acute and chronic effects of aspirin toxicity and their treatment. *Arch Intern Med* 1981;**141**(3):364–9.
- Done AK. Salicylate intoxication. Significance of measurements of salicylate in blood in cases of acute ingestion. *Pediatrics* 1960;**26**:800–7.
- Hill JB. Salicylate intoxication. *N Engl J Med* 1973;**288**(21):1110–3.
- Curry SC, Pizon AF, Riley BD, Gerkin RD, Bikin DS. Effect of intravenous albumin infusion on brain salicylate concentration. *Acad Emerg Med* 2007;**14**(6):508–14.
- Feldman MD, Behar M. A case of massive diphenhydramine abuse and withdrawal from use of the drug. *JAMA* 1986;**255**(22):3119–20.